Letters to the Editor

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Association of apolipoprotein E polymorphism with bone mineral density in postmenopausal women with rheumatoid arthritis

Sir, Pathological bone loss can occur by marginal erosions, juxta-articular osteoporosis and generalized osteoporosis in rheumatoid arthritis (RA) [1]. Several studies demonstrated that these different types of bone involvement are similarly mediated by receptor activator of nuclear factor κB ligand (RANKL), a factor stimulating osteoclast differentiation [2, 3]. Therefore, generalized osteoporosis has been suggested as a risk factor for severe joint destruction in RA. In fact, joint erosions related to generalized osteoporosis and high Larsen scores associated strongly with bone mineral density (BMD) reduction have been found in patients with RA [4]. Osteoporosis has a multifactorial aetiology, including several candidate genes, such as the genes for α2HS-glycoprotein, the oestrogen receptor, interleukin 6, type I collagen, the vitamin D receptor, transforming growth factor β1 and apolipoprotein E (ApoE) [5]. ApoE may be linked to osteoporosis and fracture through action of vitamin K, which is an important cofactor for the carboxylation of osteocalcin. Individuals with the ApoE4 allele have an accelerated hepatic clearance of vitamin K in triglyceride-rich lipoprotein; thus, they may have a low serum vitamin K concentration available for uptake by bone cells [6]. Three codominant alleles (ApoE2, ApoE3 and ApoE4) are common in humans and several studies have focused on the deleterious influence of the ApoE4 allele on BMD and fracture risk; among postmenopausal or elderly women, those with the ApoE4 allele have lower lumbar spine or hip BMD than those without the ApoE4 allele [7, 8]. However, the relationship between ApoE genotypes and the severity of osteoporosis and joint destruction in patients with RA has not yet been clarified. Therefore, this study was designed to examine whether postmenopausal RA patients with ApoE4 allele have lower BMD than patients without the ApoE4 allele. This study also assessed the destruction of hand joints radiographically to determine the relationship between the ApoE4 allele and the severity of joint erosion in RA.

In this study, a total of 110 female patients with RA aged between 45 and 82 yr were recruited from our rheumatological clinic between 2000 and 2002. All patients were postmenopausal and were diagnosed with RA, for the first time, fulfilling the American Rheumatism Association 1987 revised criteria for RA [9]. Patients were chosen who had not received any antiresorptive therapy, DMARDs or glucocorticosteroids in the past 2 yr. All 110 patients had complete ApoE genotyping and bone density measurements before the treatment of RA and osteoporosis. ApoE genotypes were analysed by gel electrophoresis following the Amplified Refractory Mutation System (ARMS) polymerase chain reaction (PCR) method [10]. BMD was measured in the lumbar spine (L2–L4) and bilaterally in the femoral neck and greater trochanter using dual-energy X-ray absorptiometry (DEXA; Prodigy; GE Lunar Corporation, Wl, USA). Plain radiographs of the hands and wrists were obtained and joint destruction was evaluated by the method described by Larsen [11]. Patient informed consent was obtained verbally; no written informed consent was required. The study was approved by the Medical Ethics Committee of the Chonbuk National University Hospital and conducted according to the principles of the Declaration of Helsinki.

The ApoE genotypes were analysed in all 110 postmenopausal women with RA. The genotypic distribution in our patients was 10% for ApoE2/3 (n = 11), 63.6% for ApoE3/3 (n = 70), 23.6% for ApoE3/4 (n = 26) and 2.7% for ApoE4/4 (n = 3). The genotypes ApoE2/2 and E2/4 were not found in the population of this study. The genotype frequencies in our study were in Hardy–Weinberg equilibrium (χ² = 2.57, P = 0.765). The combined frequency for both ApoE3/4 and 4/4 genotypes was higher in the postmenopausal women with osteoporosis than in those without osteoporosis (31.4% vs 9.7%). In view of the deleterious influence of the ApoE4 allele on BMD, we classified these patients into the two groups ApoE4(+) and ApoE4(−) according to the presence or absence of the ApoE4 allele. There were no statistically significant differences in the clinical and laboratory characteristics between the ApoE4(+) and ApoE4(−) groups. Patients in the ApoE4(+) group had significantly lower BMD in the lumbar spine and the femoral greater trochanter than patients in the ApoE4(−) group. BMD in the lumbar spine of the ApoE4(+) group was 0.85±0.13 g/cm² (n = 29), whereas that of the ApoE4(−) group was 0.96±0.14 g/cm² (n = 81; P = 0.008). BMD in the femoral greater trochanter of the ApoE4(+) group was 0.69±0.12 g/cm², while that of the ApoE4(−) group was 0.74±0.12 g/cm² (P = 0.008) (Fig. 1). However, there were no significant differences in Larsen score (1.3±1.6 vs 1.4±2.0, P = 0.608) and the rate of erosive disease (72.5% vs 66.7, P = 0.608) between the ApoE4(+) and ApoE4(−) groups.

In conclusion, data from the present study show that the ApoE4 allele is closely associated with a reduced bone mass, especially in the lumbar spine and femoral greater trochanter, and the ApoE4 allele is considered to be an independent risk factor for generalized osteoporosis in postmenopausal women with RA. Therefore, we recommend that postmenopausal RA patients with the ApoE4 allele should be treated aggressively for osteoporosis to minimize severe joint destruction. However, we have not found any significant differences in Larsen score and

![Fig. 1. BMDs of lumbar (L2–4) and femoral greater trochanter in subjects with and without the ApoE4 allele. The difference in BMD according to the presence of ApoE4 allele in the two regions was statistically significant (P = 0.008; Mann–Whitney test).](https://academic.oup.com/rheumatology/article-abstract/44/8/1067/1772046/Association-of-apolipoprotein-E-polymorphism-with)
rate of erosive disease (%) between the ApoE4(+) and ApoE4(−) groups. Further prospective study is needed to compare the change in BMD and progression of joint destruction between ApoE4(+) and ApoE4(−) groups in patients with RA.

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Evidence of effective and efficient teaching and learning strategies in the education of rheumatologist ultrasonographers: evaluation from the 3rd BSR musculoskeletal ultrasonography course

Sir, Musculoskeletal ultrasonography (MUS) is an increasingly popular clinical tool in the hands of rheumatologists, with an expanding evidence base to support its use [1, 2]. However, the operator-dependent nature and level of technical expertise necessary to perform a proficient MUS assessment means that appropriate training is required [3]. Currently there is a lack of published data to guide rheumatologists who wish to be trained in MUS and an absence of an educational structure within which learning can take place [4, 5]. As part of an ongoing project to develop such an educational framework, we have developed an evidence-based, expert-derived rheumatology ultrasound curriculum containing educational outcomes that reflect both competency standards and clinical utility [6, 7]. We piloted our curriculum and competency-based educational approach at the recent British Society for Rheumatology (BSR) course on MUS, and would like to report the results of our evaluation, with the aim of providing helpful information to inform future MUS training and practice.

Informed by our expanding educational database, we introduced a number of specific learning and teaching strategies (Table 1), which have not been formally employed on previous courses. Fundamental to our approach, and reflecting the evolving nature of educating rheumatologists in MUS, was a commitment to evaluation. A previous report from the first BSR course examined perceptions of training and development of MUS in rheumatology practice [8]. We aimed to assess the efficiency and effectiveness of our educational strategy in the attainment of our predetermined learning outcomes [9]. We used the evaluation model developed by Kirkpatrick [10] with a two-level strategy employing qualitative and quantitative techniques. Level 1 aimed to ascertain learner perceptions and levels of satisfaction and thereby the efficiency of the educational process. This was measured by an anonymous structured questionnaire requiring free-text or graded responses (1–5 Likert scale), administered at the end of the course. Level 2 assessed any change in knowledge or skills, to determine the effectiveness of our strategies. This was measured by an anonymous written test consisting of multiple-choice and short-answer questions, taken immediately before (pre-test) and after the course (post-test). Pre-course educational material was withheld until the initial examination had been conducted, to maximize test validity. Ethical approval was not required for this study.

Forty-six delegates attended the course; 77% were rheumatologists (51% specialist registrars, 35% consultants, 14% non-consultant career grades) and 23% from other disciplines (physiotherapy, podiatry, general practice, orthopaedics). Fifty-two per cent had no prior MUS experience, 41% reported some exposure and 7% confirmed regular MUS practice. Ninety-six per cent (level 1) and 80% (level 2) of delegates submitted completed evaluation forms.

The results from our level 1 evaluation demonstrated an excellent overall satisfaction rating (median Likert score 5/5; range 3–5) and confidence scores (median 4.5/5; range 3–5). Indeed, median scores ranged from 4/5 to 5/5 for all aspects of the educational process. Consistent themes were identified from the qualitative data. Areas reported to work well included: the practical emphasis of teaching; amount of time dedicated to hands-on scanning; small group size containing delegates with matched abilities, facilitating discussion and interpersonal learning; rotation between different tutors; exposure to an appropriate mix of normal MUS anatomy and pathology; timing and duration of teaching sessions. Areas for potential improvement included provision of additional precourse preparatory information; standardization of teaching sessions between tutors to ensure uniformity of information and teaching style to mirror information provided in the study guide; inclusion of a specific orientation session to provide instruction in machine operation and basic MUS anatomy, rather than integrating this into the general teaching. Delegates were asked to speculate as to the effect of the course on their future practice. The majority was motivated to continue to learn and develop their MUS skills.